INTERNATIONAL SEARCH REPORT

Intern[illegible]l Application No
PCT/GB2005/000594

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/11 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUBOTA H ET AL: "Retinoid X receptor alpha and retinoic acid receptor gamma mediate expression of genes encoding tight-junction proteins and barrier function in F9 cells during visceral endodermal differentiation." EXPERIMENTAL CELL RESEARCH. 1 FEB 2001, vol. 263, no. 1, 1 February 2001 (2001-02-01), pages 163-172, XP002339187 ISSN: 0014-4827 abstract -/--	1-4,10, 15,16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2005	22/12/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Interr ... al Application No
PCT/GB2005/000594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 26 February 1997 (1997-02-26), MULLER A ET AL: "Retinoic acid and N-(4-hydroxy-phenyl) retinamide suppress growth of esophageal squamous carcinoma cell lines." XP002339190 Database accession no. NLM9065807 abstract & CANCER LETTERS. 26 FEB 1997, vol. 113, no. 1-2, 26 February 1997 (1997-02-26), pages 95-101, ISSN: 0304-3835	1
X	WO 98/08546 A (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE M; CENTRE NATIONAL DE) 5 March 1998 (1998-03-05) abstract page 8, line 11 - page 9, line 2 page 10, lines 6-28 page 18, line 1 - page 19, line 23	1
X	WO 02/28810 A (F. HOFFMANN-LA ROCHE AG) 11 April 2002 (2002-04-11) the whole document	1
X	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 2002, NIEDERREITHER K ET AL: "Genetic evidence that oxidative derivatives of retinoic acid are not involved in retinoid signaling during mouse development" XP002339191 Database accession no. EMB-2002292503 abstract & NATURE GENETICS 2002 UNITED STATES, vol. 31, no. 1, 2002, pages 84-88, ISSN: 1061-4036	1
X	SAMPLINER R E ET AL: "A PHASE II TRIAL OF 13-CIS RETINOIC ACID (ISOTRETINOIN) IN BARRETT'S ESOPHAGUS" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, vol. 94, no. 5, PART 2, 1988, page A396, XP008048800 ISSN: 0016-5085 abstract	1,2,5,7, 8,10-12, 14

-/--

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB2005/000594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GAREWAL H ET AL: "EFFECT OF POTENTIAL DIFFERENTIATING AGENTS ON THE GROWTH OF BARRETT'S ESOPHAGUS-DERIVED EPITHELIAL CELL CULTURES" CLINICAL RESEARCH, THOROFARE, NJ, US, vol. 36, no. 1, 1988, page 131A, XP008048799 ISSN: 0009-9279 abstract	1,2,5,7, 8,10-12, 14
X	LORD R V N ET AL: "RETINOIC ACID RECEPTOR-ALPHA MESSENGER RNA EXPRESSION IS INCREASED AND RETINOIC ACID RECEPTOR-GAMMA EXPRESSION IS DECREASED IN BARRETT'S INTESTINAL METAPLASIA, DYSPLASIA, ADENOCARCINOMA SEQUENCE" SURGERY, C.V. MOSBY CO., ST. LOUIS,, US, vol. 129, no. 3, March 2001 (2001-03), pages 267-276, XP008048797 ISSN: 0039-6060 the whole document	1,2,5,7, 8,10-12, 14
X	GAREWAL H S ET AL: "CHEMOPREVENTIVE STUDIES IN BARRETT'S ESOPHAGUS: A MODEL PREMALIGNANT LESION FOR ESOPHAGEAL ADENOCARCINOMA" JOURNAL OF THE NATIONAL CANCER INSTITUTE, US DEPT. OF HEALTH, EDICATIONAND WELFARE, PUBLIC HEALTH, US, vol. 13, 1992, pages 51-54, XP008048870 ISSN: 0027-8874 abstract	1,2,5,7, 8,10-12, 14
X	TSAI P I ET AL: "Retinoic acid receptor expression in Barrett's esophagus and Berrett's associated adenocarcinomas" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 40, March 1999 (1999-03), page 309, XP001118453 & 90TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH; PHILADELPHIA, PENNSYLVANIA, USA; APRIL 10-14, 1999 ISSN: 0197-016X abstract	1,2,5,7, 8,10-12, 14

-/—

INTERNATIONAL SEARCH REPORT

Inter al Application No
PC[illegible]2005/000594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GAREWAL H ET AL: "STUDIES ON BARRETT'S ESOPHAGUS A UNIQUE METAPLASTIC PREMALIGNANT LESION FOR ADENOCARCINOMA" PREVENTIVE MEDICINE, vol. 17, no. 2, 1988, page 244, XP008048790 & 12TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF PREVENTIVE ONCOLOGY, BETHESDA, MARYLAND, USA, MARCH 1 ISSN: 0091-7435 abstract	1,2,5,7, 8,10-12, 14
X	JETTEN A M ET AL: "Retinoic acid and substratum regulate the differentiation of rabbit tracheal epithelial cells into squamous and secretory phenotype. Morphological and biochemical characterization." LABORATORY INVESTIGATION; A JOURNAL OF TECHNICAL METHODS AND PATHOLOGY. JUN 1987, vol. 56, no. 6, June 1987 (1987-06), pages 654-664, XP008056495 ISSN: 0023-6837 abstract	3-5,10, 15,16
X	SHINDOH M ET AL: "PREVENTION OF CARCINOMA IN SITU OF HUMAN PAPILLOMAVIRUS TYPE 16-IMMORTALIZED HUMAN ENDOCERVICAL CELLS BY RETINOIC ACID IN ORGANOTYPE RAFT CULTURE" OBSTETRICS AND GYNECOLOGY, NEW YORK, NY, US, vol. 85, no. 5, PART 1, May 1995 (1995-05), pages 721-728, XP008056461 ISSN: 0029-7844 abstract	15,16
X	DARWICHE N ET AL: "Specificity of retinoid receptor gene expression in mouse cervical epithelia." ENDOCRINOLOGY. MAY 1994, vol. 134, no. 5, May 1994 (1994-05), pages 2018-2025, XP008056467 ISSN: 0013-7227 abstract	15,16

-/--

INTERNATIONAL SEARCH REPORT

Interr··· al Application No
PCT/GB2005/000594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REARICK J I ET AL: "Effect of substratum and retinoids upon the mucosecretory differentiation of airway epithelial cells in vitro." ENVIRONMENTAL HEALTH PERSPECTIVES. MAR 1989, vol. 80, March 1989 (1989-03), pages 229-237, XP008056499 ISSN: 0091-6765 abstract; figures 4,5; table 1	3,4,10, 15,16
X	CASTONGUAY A ET AL: "Expression of xenobiotic-metabolizing enzymes in cultured rat tracheal epithelial cells." ENVIRONMENTAL HEALTH PERSPECTIVES. MAR 1995, vol. 103, no. 3, March 1995 (1995-03), pages 254-258, XP008056468 ISSN: 0091-6765 abstract; figure 1	3,4,10, 15,16
X	BIESALSKI H K ET AL: "Topical application of vitamin A reverses metaplasia of rat vaginal epithelium: a rapid and efficient approach to improve mucosal barrier function." EUROPEAN JOURNAL OF MEDICAL RESEARCH. 28 SEP 2001, vol. 6, no. 9, 28 September 2001 (2001-09-28), pages 391-398, XP008056473 ISSN: 0949-2321 the whole document	3,4,10, 15,16
X	WAN X ET AL: "Synthetic retinoid CD437 induces apoptosis of esophageal squamous HET-1A cells through the caspase-3-dependent pathway." ANTICANCER RESEARCH. 2001 JUL-AUG, vol. 21, no. 4A, July 2001 (2001-07), pages 2657-2663, XP008056474 ISSN: 0250-7005 abstract	3,4,10, 16

-/--

INTERNATIONAL SEARCH REPORT

Inten al Application No
PCT/GB2005/000594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KHURI F R ET AL: "Modulation of proliferating cell nuclear antigen in the bronchial epithelium of smokers." CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION : A PUBLICATION OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, COSPONSORED BY THE AMERICAN SOCIETY OF PREVENTIVE ONCOLOGY. APR 2001, vol. 10, no. 4, April 2001 (2001-04), pages 311-318, XP008056466 ISSN: 1055-9965 abstract	15,16
X	VARANI J ET AL: "A direct comparison of pharmacologic effects of retinoids on skin cells in vitro and in vivo." SKIN PHARMACOLOGY : THE OFFICIAL JOURNAL OF THE SKIN PHARMACOLOGY SOCIETY. 1991, vol. 4, no. 4, 1991, pages 254-261, XP008056480 ISSN: 1011-0283 abstract	4
X	KIKONYOGO A ET AL: "Mechanism of inhibition of aldehyde dehydrogenase by citral, a retinoid antagonist." EUROPEAN JOURNAL OF BIOCHEMISTRY / FEBS. JUN 1999, vol. 262, no. 3, June 1999 (1999-06), pages 704-712, XP008056514 ISSN: 0014-2956 the whole document	6-9
X	WHITE J A ET AL: "Identification of the human cytochrome P450, P450RAI-2, which is predominantly expressed in the adult cerebellum and is responsible for all-trans-retinoic acid metabolism." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. 6 JUN 2000, vol. 97, no. 12, 6 June 2000 (2000-06-06), pages 6403-6408, XP002168088 ISSN: 0027-8424 the whole document	6-8

-/--

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB2005/000594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG YUANPING ET AL: "Cloning of rat cytochrome P450RAI (CYP26) cDNA and regulation of its gene expression by all-trans-retinoic acid in vivo." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS. 15 MAY 2002, vol. 401, no. 2, 15 May 2002 (2002-05-15), pages 235-243, XP008056506 ISSN: 0003-9861 abstract	6
Y	KLAASSEN I ET AL: "Enhanced turnover of all-trans-retinoic acid and increased formation of polar metabolites in head and neck squamous cell carcinoma lines compared with normal oral keratinocytes." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. APR 2001, vol. 7, no. 4, April 2001 (2001-04), pages 1017-1025, XP8056504 ISSN: 1078-0432 abstract	6
Y	TAIMI MOHAMMED ET AL: "A novel human cytochrome P450, CYP26C1, involved in metabolism of 9-cis and all-trans isomers of retinoic acid." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 2 JAN 2004, vol. 279, no. 1, 2 January 2004 (2004-01-02), pages 77-85, XP008056509 ISSN: 0021-9258 the whole document	6
Y	MIRY-Y-LOPEZ R ET AL: "RETINOL CONVERSION TO RETINOIC ACID IS IMPAIRED IN BREAST CANCER CELL LINES RELATIVE TO NORMAL CELLS" JOURNAL OF CELLULAR PHYSIOLOGY, LISS, NEW YORK, NY, US, vol. 185, no. 2, 2000, pages 302-309, XP001062760 ISSN: 0021-9541 the whole document	6

-/--

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB2005/000594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LAMPEN A ET AL: "Metabolism of vitamin A and its active metabolite all-trans-retinoic acid in small intestinal enterocytes." THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS. DEC 2000, vol. 295, no. 3, December 2000 (2000-12), pages 979-985, XP008056505 ISSN: 0022-3565 abstract	6-10

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/GB2005/000594

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5,7-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 5,7-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 17

Claim 17 was not searched because it does not contain technical features

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 7-10 (partially) 1,2,5,11-14

Use of a retinoic acid antagonist in the manufacture of a medicament for the treatment or prevention of Barrett's oesophagus.

---

2. claims: 7-10 (partially) 3,4,15,16

Use of a retinoic acid antagonist in the conversion of columnar epithelium to squamous epithelium and in the induction or maintenance of squamous epithelium.

---

3. claims: 7-10 (partially) 6

Use of a retinoic acid antagonist in the downregulation of CYP26A1.

INTERNATIONAL SEARCH REPORT

rmation on patent family members

Inter[illegible]l Application No
PCT/GB2005/000594

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9808546	A	05-03-1998	AT	236654 T	15-04-2003
			AU	731060 B2	22-03-2001
			AU	4167497 A	19-03-1998
			CA	2263817 A1	05-03-1998
			DE	69720745 D1	15-05-2003
			DE	69720745 T2	26-02-2004
			EP	0928200 A2	14-07-1999
			ES	2196361 T3	16-12-2003
			JP	2001500486 T	16-01-2001
			NO	990912 A	27-04-1999
WO 0228810	A	11-04-2002	AU	8991301 A	15-04-2002
			AU	2001289913 A2	15-04-2002
			BR	0114344 A	01-07-2003
			CA	2422805 A1	11-04-2002
			CN	1468207 A	14-01-2004
			CZ	20031216 A3	15-10-2003
			EP	1324970 A2	09-07-2003
			HR	20030230 A2	28-02-2005
			HU	0303006 A2	29-12-2003
			JP	2004510728 T	08-04-2004
			MA	26950 A1	20-12-2004
			MX	PA03002861 A	14-07-2003
			NO	20031480 A	20-05-2003
			NZ	524603 A	29-10-2004
			PL	362671 A1	02-11-2004
			ZA	200301978 A	25-06-2004